United States Patent Application for:

AEROSOLIZATION APPARATUS WITH ROTATING CAPSULE

Inventors:

1) William W. Alston
2336 Westmoreland Drive
San Jose, CA 95124
Citizenship: USA

Assignee:	Nektar Therapeutics (formerly Inhale Therapeutic Systems, Inc.) 150 Industrial Road San Carlos, CA 94070
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Kathy Honnert
Name of Person Mailing Paper

Kathy Honnert
Signature of Person Mailing Paper

Aerosolization Apparatus with Rotating Capsule

This application claims the benefit U.S. Provisional Patent Application Serial No. 60/437,225 filed on December 31, 2002, which is incorporated herein by reference in its entirety.

BACKGROUND

The need for effective therapeutic treatment of patients has resulted in the development of a variety of pharmaceutical formulation delivery techniques. One traditional technique involves the oral delivery of a pharmaceutical formulation in the form of a pill, capsule, elixir, or the like. However, oral delivery can in some cases be undesirable. For example, many pharmaceutical formulations may be degraded in the digestive tract before they can be effectively absorbed by the body. Inhaleable drug delivery, where an aerosolized pharmaceutical formulation is orally or nasally inhaled by a patient to deliver the formulation to the patient's respiratory tract, has proven to be a particularly effective and/or desirable alternative. For example, in one inhalation technique, an aerosolized pharmaceutical formulation provides local therapeutic relief to a portion of the respiratory tract, such as the lungs, to treat diseases such as asthma, emphysema, and cystic fibrosis. In another inhalation technique, a pharmaceutical formulation is delivered deep within a patient's lungs where it may be absorbed into the blood stream. Many types of inhalation devices exist including devices that aerosolize a dry powder pharmaceutical formulation.

One type of inhalation device aerosolizes a pharmaceutical formulation that is stored in a capsule. For example, a dose or a portion of a dose of a dry powder pharmaceutical formulation may be stored in a capsule, and the capsule may be inserted into an aerosolization device which is capable of aerosolizing the pharmaceutical formulation. The aerosolization may be accomplished by releasing stored energy. For example, the aerosolization may be accomplished by utilizing energy supplied during the user's inhalation, such as the flow of inhaled air, to aerosolize the pharmaceutical formulation. After being inserted into the aerosolization device, the capsule is opened to expose the pharmaceutical formulation. The opening of the capsule may be performed, for example, by puncturing or tearing the capsule. When the capsule is properly opened and when

aerosolization energy is supplied, the pharmaceutical formulation is aerosolized so that it may be inhaled by the user and a dose or portion of a dose of the aerosolized pharmaceutical formulation may be delivered to the user's respiratory tract.

The size and quality of the dose delivered to the user is dependent on the amount and condition of aerosolizable pharmaceutical formulation that exits the capsule. However, in conventional aerosolization devices, the amount and condition of the aerosolizable pharmaceutical formulation may vary from use to use and/or from user to user. For example, sometimes it is difficult to cause large amounts of the pharmaceutical formulation to exit the capsule when a user is unable to generate a high flow rate inhalation. In addition, it is sometimes difficult to cause large amounts of the pharmaceutical formulation to exit the capsule during very high flow rate inhalations due to compaction of the pharmaceutical formulation within the capsule. The inefficient release of pharmaceutical formulation can be costly and can result in the necessity for numerous operations of the device in order to achieve a desire dosage. In some circumstances, the pharmaceutical formulation exits the capsule in agglomerated form, the agglomerations being undesirably large for inhalation therapy.

Therefore, it is desirable to be able to aerosolize a pharmaceutical formulation in a consistent manner. It is further desirable to be able to aerosolize a pharmaceutical formulation in a manner that extracts an increased amount of the pharmaceutical formulation from a receptacle. It is also desirable to be able to aerosolize a pharmaceutical formulation in a more deagglomerated form.

SUMMARY

The present invention satisfies these needs. In one aspect of the invention, a receptacle rotates within an aerosolization chamber in an improved manner.

In another aspect of the invention, an aerosolization apparatus comprises a body defining an inlet opening, an outlet opening, and an aerosolization chamber between the inlet opening and the outlet opening, wherein the aerosolization chamber is adapted to receive an

elongated receptacle containing a pharmaceutical formulation and wherein the elongated receptacle rotates end-over-end about an axis substantially orthogonal to an axis passing through the outlet opening when air or gas flows through the body.

In another aspect of the invention, an aerosolization apparatus is provided for delivering an aerosolized pharmaceutical formulation to a user's respiratory tract. The apparatus comprises a body defining an inlet opening, an outlet opening, and an aerosolization chamber between the inlet opening and the outlet opening, wherein the aerosolization chamber is adapted to receive an elongated receptacle containing a pharmaceutical formulation and wherein the elongated receptacle rotates end-over-end about an axis substantially orthogonal to an axis parallel to an inhalation direction when the user inhales to cause air or gas to pass through the body.

DRAWINGS

These features, aspects, and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying drawings which illustrate exemplary features of the invention. However, it is to be understood that each of the features can be used in the invention in general, not merely in the context of the particular drawings, and the invention includes any combination of these features, where:

Figure 1A is a schematic sectional side view of an aerosolization apparatus in an initial position;

Figure 1B is a schematic sectional side view of the aerosolization apparatus shown in Figure 1A at the beginning a receptacle opening process;

Figure 1C is a schematic sectional side view of the aerosolization apparatus shown in Figure 1A during the a receptacle opening process;

Figure 1D is a schematic sectional side view of the aerosolization apparatus shown in Figure 1A during the beginning of an aerosolization process;

Figure 1E is a schematic sectional side view of the aerosolization apparatus shown in Figure 1A during the aerosolization process;

Figure 2A is a schematic sectional side view of another version of an aerosolization apparatus of the invention;

Figure 2B is a schematic sectional top view of a portion of the version of an aerosolization apparatus shown in Figure 2A.

DESCRIPTION

The present invention relates to an aerosolization apparatus. In particular, the invention relates to an aerosolization apparatus capable of aerosolizing a pharmaceutical formulation contained in a receptacle, such as a capsule. Although the process is illustrated in the context of aerosolizing a dry powder pharmaceutical formulation for inhalation, the present invention can be used in other processes and should not be limited to the examples provided herein.

An aerosolization apparatus **100** according to the present invention is shown schematically in Figure 1A. The aerosolization apparatus **100** comprises a housing **105** defining a chamber **110** having one or more air inlets **115** and one or more air outlets **120**. The chamber **110** is sized to receive a receptacle **125** which contains an aerosolizable pharmaceutical formulation. An opening mechanism **130** comprises an opening member **135** that is moveable within the chamber **110**. Near or adjacent the outlet **120** is an end section **140** that may be sized and shaped to be received in a user's mouth or nose so that the user may inhale through an opening **145** in the end section **140** that is in communication with the outlet **120**.

The aerosolization apparatus **100** utilizes air flowing through the chamber **110** to aerosolize the pharmaceutical formulation in the receptacle **125**. For example, Figures 1A through 1E illustrate the operation of a version of an aerosolization apparatus **100** where air flowing through

the inlet **115** is used to aerosolize the pharmaceutical formulation and the aerosolized pharmaceutical formulation flows through the outlet **120** so that it may be delivered to the user through the opening **145** in the end section **140**. The aerosolization apparatus **100** is shown in its initial condition in Figure 1A. The receptacle **125** is positioned within the chamber **110** and the pharmaceutical formulation is secured within the receptacle **125**.

To use the aerosolization apparatus **100**, the pharmaceutical formulation in the receptacle **125** is exposed to allow it to be aerosolized. In the version of Figures 1A though 1E, the opening mechanism **130** is advanced within the chamber **110** by applying a force **150** to the opening mechanism **130**. For example, a user may press against a surface **155** of the opening mechanism **130** to cause the opening mechanism **130** to slide within the housing **105** so that the opening member **135** contacts the receptacle **125** in the chamber **110**, as shown in Figure 1B. By continuing to apply the force **150**, the opening member **135** is advanced to abut the wall of the receptacle **125** or to extend into the wall of the receptacle **125**, as shown in Figure 1C. The opening member may comprise one or more blunt or sharp tips **152** that contact the receptacle **125** in a manner that provides an opening into the receptacle **125**. Examples of sharpened opening mechanisms are described in U.S. Patent 4,069,819; in U.S. Patent 4,995,385; and in U.S. Patent 3,991,761, all of which are incorporated herein by reference in their entireties. The opening mechanism **130** is then retracted to the position shown in Figure 1D, leaving an opening **160** through the wall of the receptacle **125** to expose the pharmaceutical formulation in the receptacle **125**. Alternatively, a non-puncturing opening mechanism may be used, such as the mechanism described in U.S. Provisional Patent Application Serial No. 60/437,254 filed on December 31m 2002 and in the corresponding non-provisional application claiming the benefit thereof, attorney docket number 0136.00, both of which are incorporated herein by reference in their entireties.

Air or other gas then flows through an inlet **115**, as shown by arrows **165** in Figure 1E. The flow of air causes the pharmaceutical formulation to be aerosolized. When the user inhales **170** through the end section **140** the aerosolized pharmaceutical formulation is delivered to the user's respiratory tract. In one version, the air flow **165** may be caused by the user's inhalation **170**. In another version, compressed air or other gas may be ejected into the inlet **115** from a source of pressurized gas to cause the aerosolizing air flow **165**.

As can be seen in Figure 1E, the chamber **110** of the aerosolization apparatus **100** is shaped so that the receptacle **125** rotates within the chamber **110**. The airflow is designed so that the receptacle **125** rotates in the direction of the arrows **175**, that is in an end-over-end manner. The rotation is substantially about an axis that is substantially orthogonal to the inhalation direction **170** and/or to the direction through the outlet **120**. In another version, the rotation is substantially about an axis that is substantially orthogonal to the inhalation direction **170** and/or to the direction through the outlet **120** and where a central longitudinal axis of the receptacle remains substantially within a vertical plane. By "substantially" it is meant within a deviation of 30 degrees.

The rotational motion of the receptacle shown in Figure 1E allows for improved aerosolization. The rotation forces the pharmaceutical formulation in the receptacle **125** to be force outwardly through the opening **160**. Accordingly, an increased amount of the pharmaceutical formulation is ejected from the receptacle **125** and is entrained in the airflow. In addition, the forces acting on the pharmaceutical formulation provide improved deagglomeration of the pharmaceutical formulation. In one version, the inlets **115** may be designed to encourage the end-over-end motion of the capsule. For example, an inlet may be formed so as to cause the air flow to take on the path shown **166** in section in Figure 1E.

A version of an aerosolization apparatus **100** having a chamber **110** accommodating a rotating receptacle **125** is shown in Figures 2A and 2B. Figure 2A shows a cross-sectional side view of the aerosolization apparatus **100** in use. As can be seen, the aerosolization chamber **110** in this version is substantially circular. One or more inlets **115** are provided to create a circular airflow path that causes the receptacle **125** to rotate as discussed above. As can be seen in Figure 2B, which is a top sectional view through the chamber **110**, a constraining member **200** may be provided to constrain the receptacle **125** to the desired rotation. In one version, a sidewall **205** of the chamber may removable or may be hinged to the chamber **110** to allow access to the chamber **110** for insertion of the receptacle **125** thereinto. The one or more openings **160** into the receptacle **125** may be provided before insertion of the receptacle **125** into the chamber **110** or may be created within the chamber **110**. For example, the openings **160** may be created by creating weakened portions on the receptacle **125** and then applying a force to the receptacle **125** to cause the

weakened portions to open, as described in the aforementioned U.S. Provisional Patent Application Serial No. 60/437,254 filed on December 31m 2002 and in the aforementioned corresponding non-provisional application claiming the benefit thereof, attorney docket number 0136.00. Alternatively, a sharpened member may be provided in a portion of the chamber to create the opening in the receptacle as described in the aforementioned U.S. Patent 3,991,761.

In another version, the aerosolization of the pharmaceutical formulation may be accomplished by pressurized gas flowing through the one or more inlets **115**, as described for example in US Patent 5,458,135, U.S. Patent 5,785,049, and U.S. Patent 6,257,233, or propellant, as described in PCT Publication WO 00/72904 and U.S, Patent 4,114,615. All of the above references being incorporated herein by reference in their entireties.

In one version, the receptacle **125** comprises a capsule type receptacle. The capsule may be of a suitable shape, size, and material to contain the pharmaceutical formulation and to provide the pharmaceutical formulation in a usable condition. For example, the capsule may comprise a wall which comprises a material that does not adversely react with the pharmaceutical formulation. In addition, the wall may comprise a material that allows the capsule to be opened to allow the pharmaceutical formulation to be aerosolized. In one version, the wall comprises one or more of gelatin, hydroxypropyl methylcellulose (HPMC), polyethyleneglycol-compounded HPMC, hydroxyproplycellulose, agar, or the like. Alternatively or additionally, the capsule wall may comprise a polymeric material, such as polyvinyl chloride (PVC). In one version, the capsule may comprise telescopically ajoined sections, as described for example in U.S. Patent 4,247,066 which is incorporated herein by reference in its entirety. The interior of the capsule may be filled with a suitable amount of the pharmaceutical formulation, and the size of the capsule may be selected to adequately contain a desired amount of the pharmaceutical formulation. The sizes generally range from size 5 to size 000 with the outer diameters ranging from about 4.91 mm to 9.97 mm, the heights ranging from about 11.10 mm to about 26.14 mm, and the volumes ranging from about 0.13 ml to about 1.37 ml, respectively. Suitable capsules are available commercially from, for example, Shionogi Qualicaps Co. in Nara, Japan and Capsugel in Greenwood, South Carolina. After filling, a top portion may be placed over the bottom portion to form the a capsule shape and to contain the powder within the capsule, as described in U.S. Patent 4,846,876, U.S. Patent 6,357,490, and in the

PCT application WO 00/07572 published on February 17, 2000, all of which are incorporated herein by reference in their entireties.

In a preferred version, the invention provides a system and method for aerosolizing a pharmaceutical formulation and delivering the pharmaceutical formulation to the respiratory tract of the user, and in particular to the lungs of the user. The pharmaceutical formulation may comprise powdered medicaments, liquid solutions or suspensions, and the like, and may include an active agent.

The active agent described herein includes an agent, drug, compound, composition of matter or mixture thereof which provides some pharmacologic, often beneficial, effect. This includes foods, food supplements, nutrients, drugs, vaccines, vitamins, and other beneficial agents. As used herein, the terms further include any physiologically or pharmacologically active substance that produces a localized or systemic effect in a patient. An active agent for incorporation in the pharmaceutical formulation described herein may be an inorganic or an organic compound, including, without limitation, drugs which act on: the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system, and the central nervous system. Suitable active agents may be selected from, for example, hypnotics and sedatives, psychic energizers, tranquilizers, respiratory drugs, anticonvulsants, muscle relaxants, antiparkinson agents (dopamine antagnonists), analgesics, anti-inflammatories, antianxiety drugs (anxiolytics), appetite suppressants, antimigraine agents, muscle contractants, anti-infectives (antibiotics, antivirals, antifungals, vaccines) antiarthritics, antimalarials, antiemetics, anepileptics, bronchodilators, cytokines, growth factors, anti-cancer agents, antithrombotic agents, antihypertensives, cardiovascular drugs, antiarrhythmics, antioxicants, anti-asthma agents, hormonal agents including contraceptives, sympathomimetics, diuretics, lipid regulating agents, antiandrogenic agents, antiparasitics, anticoagulants, neoplastics, antineoplastics, hypoglycemics, nutritional agents and supplements, growth supplements, antienteritis agents, vaccines, antibodies, diagnostic agents, and

contrasting agents. The active agent, when administered by inhalation, may act locally or systemically.

The active agent may fall into one of a number of structural classes, including but not limited to small molecules, peptides, polypeptides, proteins, polysaccharides, steroids, proteins capable of eliciting physiological effects, nucleotides, oligonucleotides, polynucleotides, fats, electrolytes, and the like.

Examples of active agents suitable for use in this invention include but are not limited to one or more of calcitonin, amphotericin B, erythropoietin (EPO), Factor VIII, Factor IX, ceredase, cerezyme, cyclosporin, granulocyte colony stimulating factor (GCSF), thrombopoietin (TPO), alpha-1 proteinase inhibitor, elcatonin, granulocyte macrophage colony stimulating factor (GMCSF), growth hormone, human growth hormone (HGH), growth hormone releasing hormone (GHRH), heparin, low molecular weight heparin (LMWH), interferon alpha, interferon beta, interferon gamma, interleukin-1 receptor, interleukin-2, interleukin-1 receptor antagonist, interleukin-3, interleukin-4, interleukin-6, luteinizing hormone releasing hormone (LHRH), factor IX, insulin, pro-insulin, insulin analogues (e.g., mono-acylated insulin as described in U.S. Patent No. 5,922,675, which is incorporated herein by reference in its entirety), amylin, C-peptide, somatostatin, somatostatin analogs including octreotide, vasopressin, follicle stimulating hormone (FSH), insulin-like growth factor (IGF), insulintropin, macrophage colony stimulating factor (M-CSF), nerve growth factor (NGF), tissue growth factors, keratinocyte growth factor (KGF), glial growth factor (GGF), tumor necrosis factor (TNF), endothelial growth factors, parathyroid hormone (PTH), glucagon-like peptide thymosin alpha 1, IIb/IIIa inhibitor, alpha-1 antitrypsin, phosphodiesterase (PDE) compounds, VLA-4 inhibitors, bisphosponates, respiratory syncytial virus antibody, cystic fibrosis transmembrane regulator (CFTR) gene, deoxyreibonuclease (Dnase), bactericidal/permeability increasing protein (BPI), anti-CMV antibody, 13-cis retinoic acid, macrolides such as erythromycin, oleandomycin, troleandomycin, roxithromycin, clarithromycin, davercin, azithromycin, flurithromycin, dirithromycin, josamycin, spiromycin, midecamycin, leucomycin, miocamycin, rokitamycin, andazithromycin, and swinolide A; fluoroquinolones such as ciprofloxacin, ofloxacin, levofloxacin, trovafloxacin, alatrofloxacin, moxifloxicin, norfloxacin, enoxacin, grepafloxacin, gatifloxacin, lomefloxacin, sparfloxacin, temafloxacin, pefloxacin,

amifloxacin, fleroxacin, tosufloxacin, prulifloxacin, irloxacin, pazufloxacin, clinafloxacin, and sitafloxacin, aminoglycosides such as gentamicin, netilmicin, paramecin, tobramycin, amikacin, kanamycin, neomycin, and streptomycin, vancomycin, teicoplanin, rampolanin, mideplanin, colistin, daptomycin, gramicidin, colistimethate, polymixins such as polymixin B, capreomycin, bacitracin, penems; penicillins including penicllinase-sensitive agents like penicillin G, penicillin V, penicillinase-resistant agents like methicillin, oxacillin, cloxacillin, dicloxacillin, floxacillin, nafcillin; gram negative microorganism active agents like ampicillin, amoxicillin, and hetacillin, cillin, and galampicillin; antipseudomonal penicillins like carbenicillin, ticarcillin, azlocillin, mezlocillin, and piperacillin; cephalosporins like cefpodoxime, cefprozil, ceftbuten, ceftizoxime, ceftriaxone, cephalothin, cephapirin, cephalexin, cephradrine, cefoxitin, cefamandole, cefazolin, cephaloridine, cefaclor, cefadroxil, cephaloglycin, cefuroxime, ceforanide, cefotaxime, cefatrizine, cephacetrile, cefepime, cefixime, cefonicid, cefoperazone, cefotetan, cefmetazole, ceftazidime, loracarbef, and moxalactam, monobactams like aztreonam; and carbapenems such as imipenem, meropenem, pentamidine isethiouate, albuterol sulfate, lidocaine, metaproterenol sulfate, beclomethasone diprepionate, triamcinolone acetamide, budesonide acetonide, fluticasone, ipratropium bromide, flunisolide, cromolyn sodium, ergotamine tartrate and where applicable, analogues, agonists, antagonists, inhibitors, and pharmaceutically acceptable salt forms of the above. In reference to peptides and proteins, the invention is intended to encompass synthetic, native, glycosylated, unglycosylated, pegylated forms, and biologically active fragments and analogs thereof.

Active agents for use in the invention further include nucleic acids, as bare nucleic acid molecules, vectors, associated viral particles, plasmid DNA or RNA or other nucleic acid constructions of a type suitable for transfection or transformation of cells, i.e., suitable for gene therapy including antisense. Further, an active agent may comprise live attenuated or killed viruses suitable for use as vaccines. Other useful drugs include those listed within the Physician's Desk Reference (most recent edition).

The amount of active agent in the pharmaceutical formulation will be that amount necessary to deliver a therapeutically effective amount of the active agent per unit dose to achieve the desired result. In practice, this will vary widely depending upon the particular agent, its

activity, the severity of the condition to be treated, the patient population, dosing requirements, and the desired therapeutic effect. The composition will generally contain anywhere from about 1% by weight to about 99% by weight active agent, typically from about 2% to about 95% by weight active agent, and more typically from about 5% to 85% by weight active agent, and will also depend upon the relative amounts of additives contained in the composition. The compositions of the invention are particularly useful for active agents that are delivered in doses of from 0.001 mg/day to 100 mg/day, preferably in doses from 0.01 mg/day to 75 mg/day, and more preferably in doses from 0.10 mg/day to 50 mg/day. It is to be understood that more than one active agent may be incorporated into the formulations described herein and that the use of the term "agent" in no way excludes the use of two or more such agents.

The pharmaceutical formulation may comprise a pharmaceutically acceptable excipient or carrier which may be taken into the lungs with no significant adverse toxicological effects to the subject, and particularly to the lungs of the subject. In addition to the active agent, a pharmaceutical formulation may optionally include one or more pharmaceutical excipients which are suitable for pulmonary administration. These excipients, if present, are generally present in the composition in amounts ranging from about 0.01 % to about 95% percent by weight, preferably from about 0.5 to about 80%, and more preferably from about 1 to about 60% by weight. Preferably, such excipients will, in part, serve to further improve the features of the active agent composition, for example by providing more efficient and reproducible delivery of the active agent, improving the handling characteristics of powders, such as flowability and consistency, and/or facilitating manufacturing and filling of unit dosage forms. In particular, excipient materials can often function to further improve the physical and chemical stability of the active agent, minimize the residual moisture content and hinder moisture uptake, and to enhance particle size, degree of aggregation, particle surface properties, such as rugosity, ease of inhalation, and the targeting of particles to the lung. One or more excipients may also be provided to serve as bulking agents when it is desired to reduce the concentration of active agent in the formulation.

Pharmaceutical excipients and additives useful in the present pharmaceutical formulation include but are not limited to amino acids, peptides, proteins, non-biological polymers, biological polymers, carbohydrates, such as sugars, derivatized sugars such as alditols, aldonic

acids, esterified sugars, and sugar polymers, which may be present singly or in combination. Suitable excipients are those provided in WO 96/32096, which is incorporated herein by reference in its entirety. The excipient may have a glass transition temperature (Tg) above about 35° C, preferably above about 40 °C, more preferably above 45° C, most preferably above about 55 °C.

Exemplary protein excipients include albumins such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, hemoglobin, and the like. Suitable amino acids (outside of the dileucyl-peptides of the invention), which may also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, tyrosine, tryptophan, and the like. Preferred are amino acids and polypeptides that function as dispersing agents. Amino acids falling into this category include hydrophobic amino acids such as leucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, and proline. Dispersibility- enhancing peptide excipients include dimers, trimers, tetramers, and pentamers comprising one or more hydrophobic amino acid components such as those described above.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), pyranosyl sorbitol, myoinositol and the like.

The pharmaceutical formulation may also include a buffer or a pH adjusting agent, typically a salt prepared from an organic acid or base. Representative buffers include organic acid salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid, Tris, tromethamine hydrochloride, or phosphate buffers.

The pharmaceutical formulation may also include polymeric excipients/additives, e.g., polyvinylpyrrolidones, derivatized celluloses such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylmethylcellulose, Ficolls (a polymeric sugar), hydroxyethylstarch, dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin and

sulfobutylether-β-cyclodextrin), polyethylene glycols, and pectin.

The pharmaceutical formulation may further include flavoring agents, taste-masking agents, inorganic salts (for example sodium chloride), antimicrobial agents (for example benzalkonium chloride), sweeteners, antioxidants, antistatic agents, surfactants (for example polysorbates such as "TWEEN 20" and "TWEEN 80"), sorbitan esters, lipids (for example phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines), fatty acids and fatty esters, steroids (for example cholesterol), and chelating agents (for example EDTA, zinc and other such suitable cations). Other pharmaceutical excipients and/or additives suitable for use in the compositions according to the invention are listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), both of which are incorporated herein by reference in their entireties.

"Mass median diameter" or "MMD" is a measure of mean particle size, since the powders of the invention are generally polydisperse (i.e., consist of a range of particle sizes). MMD values as reported herein are determined by centrifugal sedimentation, although any number of commonly employed techniques can be used for measuring mean particle size. "Mass median aerodynamic diameter" or "MMAD" is a measure of the aerodynamic size of a dispersed particle. The aerodynamic diameter is used to describe an aerosolized powder in terms of its settling behavior, and is the diameter of a unit density sphere having the same settling velocity, generally in air, as the particle. The aerodynamic diameter encompasses particle shape, density and physical size of a particle. As used herein, MMAD refers to the midpoint or median of the aerodynamic particle size distribution of an aerosolized powder determined by cascade impaction.

In one version, the powdered formulation for use in the present invention includes a dry powder having a particle size selected to permit penetration into the alveoli of the lungs, that is, preferably 10 μm mass median diameter (MMD), preferably less than 7.5 μm, and most preferably less than 5 μm, and usually being in the range of 0.1 μm to 5 μm in diameter. The delivered dose efficiency (DDE) of these powders may be greater than 30%, more preferably greater than 40%, more preferably greater than 50% and most preferably greater than 60% and the

aerosol particle size distribution is about 1.0 - 5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5 - 4.5 μm MMAD and preferably 1.5 - 4.0 μm MMAD. These dry powders have a moisture content below about 10% by weight, usually below about 5% by weight, and preferably below about 3% by weight. Such powders are described in WO 95/24183, WO 96/32149, WO 99/16419, and WO 99/16422, all of which are all incorporated herein by reference in their entireties.

Although the present invention has been described in considerable detail with regard to certain preferred versions thereof, other versions are possible, and alterations, permutations and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. For example, the cooperating components may be reversed or provided in additional or fewer number. Also, the various features of the versions herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.